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CALCIUM CALMODULIN-DEPENDENT PROTEIN KINASE II (CAMKII) VERSATILE PLAYER FOR SYNAPTIC PLASTICITY

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ABSTRACT

Calcium ions (Ca^{2+}) play significant role in signal transduction pathways. Ca^{2+} signaling is mediated through several Ca^{2+}-binding proteins, including calmodulin (CaM). CaM is a regulatory protein that modulate the activity of several signaling molecules those are crucial for synaptic plasticity including Ca^{2+}/calmodulin-dependent protein kinase or (CaM kinase II). CaMKII is a multifunctional signaling protein that comprises 1%–2% of the protein in brain. Due to its extraordinary abundance within neuronal cells, CaMKII has been believed to act as both a structural protein as well as an enzyme during synaptic plasticity. CaMKII is a key synaptic signaling protein, and involved in numerous forms of synaptic plasticity such as LTP. CaMKII has been one of the most extensively studied signaling protein that play a pivotal role in various forms of synaptic plasticity and memory in hippocampal and other neurons. The studies have shown CaMKII is involved in numerous forms of synaptic plasticity including long-term potentiation (LTP), long-term depression (LTD) and short-term potentiation (STP). These all form of plasticity forms the basis for learning, memory and cognition.

KEYWORDS: Calcium/calmodulin-dependent protein kinase II, long-term Potentiation, long-term Depression, short-term potentiation, synaptic plasticity,

INTRODUCTION:

Multifunctional, C^{a2+}/calmodulin-dependent protein kinase or (CaM kinase II) is a major mediator of calcium signaling in neurons, where it provides a molecular switch, whose activity is although triggered by Ca^{2+} but is not contingent upon its presence. Specifically, once activated by Ca^{2+}, it autophosphorylate itself at threonine 287 (T287) (Hodge, et al., 2006) and can be active long after Ca^{2+} returns to its basal levels. CaMKII is one of the most abundant proteins in neurons comprising 1-2% of the total protein concentration. The unique properties of CaMKII, including its abundance, multifunctional nature, key location and sophisticated regulation may allow the enzyme to take part in important synaptic functions, including neurotransmitter synthesis and release, modulation of ion channels activity, synaptic plasticity and gene expression (reviewed in (Braun and Schulman, 1995, Fujishiro Donai, 2006, Meyer, et al., 1992).

Although CaMKII may exert its effects either presynaptically or postsynaptically, its expression is particularly high at the postsynaptic density. There are more than 30 isoforms of CaMKII and numerous substrates, many of which are located in the postsynaptic density through which it can modify neuronal function (Fink and Meyer, 2002, Gan, et al., 2015). Postsynaptically, CaMKII enhances both non-NMDA (Kolaj, et al., 1994, Wang, et al., 2006, Yakel, et al., 1995) and NMDA currents (Gan, et al., 2015, Kitamura, et al., 1993, Kolaj, et al., 1994, Wirkner, et al., 2006) in different preparations. The potential regulation of so many proteins at postsynaptic density (PSD) strongly supports the importance of CaMKII in regulating synaptic function (Fink and Meyer, 2002). Presynaptically, CaMKII may modulate transmitter release by phosphorylating some synaptic vesicle-associated proteins for example synapsin 1. synaptophysin, synaptotagmin and the vesicle associated membrane protein (VAMP)/synaptobrevin (SYB) (Rubenstein, et al., 1993, Sudhof and Jahn, 1991). Genetic knockdown of these proteins results in the disruption of presynaptic facilitation of transmitter release (Zucker and Regehr, 2002).

CaMKII is involved in numerous forms of synaptic plasticity such as LTP (Gao, et al., 2006, Goodell, et al., 2016, Huang, et al., 1994, Juarez-Munoz, et al., 2017, Malenka, et al., 1989, Miyamoto, 2006, Myers, et al., 2017, Parsley, et al., 2007, Wu, et al., 2006), LTD (Goodell, et al., 2016, Hansel, et al., 2006, Mulkey, et al., 1993, Stevens and Wang, 1994) and PTP (Chapman, et al., 1995) short-term plasticity (Luk, et al., 2011).

CaMKII in the Brain:

A number of studies have described diverse expression patterns for each of the CaM kinase isoforms, α- and β -CaM kinase II isoforms are specifically present in neurons and are abundant in the brain; whereas γ – and δ-CaM kinase II isoforms are expressed at low levels in all tissues including the brain (Tobimatsu and Fujisawa, 1989). Moreover, the expression of γ-and β- CaM kinase II isoforms is not uniform across all regions of the brain (Miller and Kennedy, 1985). In the adult rat, α-CaM kinase II is enriched in the forebrain, leading to a α:β subunit ratio of 3:1. The level of α -CaM kinase expression is much lower in the cerebellum, resulting in a α:β subunit ratio of 1:3-4. The γ - and δ -CaM kinase II isoforms each exhibit a distinct regional distribution in rat brain (Sakagami and Kondo, 1993). Further studies have shown that CaM kinase II expression is developmentally regulated (Burkert and Duch, 2006, Sahyoun, et al., 1985). In the neonatal rat, β -CaM kinase II is expressed at a higher level than α-CaM kinase II throughout the brain. However, while β -CaM kinase expression stays almost constant thereafter, the α -CaM kinase II levels in the forebrain increase by approximately 10 fold during the second postnatal week. In addition, α- and β -CaM kinase II may also differ in their subcellular localization since mRNA for α- but not β -CaM kinase is found in the dendrites of hippocampal and cortical neurons (Burgin, et al., 1990). Then studies therefore suggest that in addition to its role in the adult brain, CaMKII may serve developmental functions. However its precise developmental role in synapse formation remains to be determined.

Structure and Activation of CaMKII:

The electron microscopy studies suggest that the holoenzyme is an oligomeric protein comprised of twelve (50-60 kDa) hetero-oligomers subunits arranged in two stacked hexameric ring (Kanaseki, et al., 1991, Kolodziej, et al., 2000). Each CaMKII subunit consists of three domains; (A) N-terminal catalytic domain, Phosphorylation site located at this domain (B) central regulatory domain consisting of two motifs which overlap, a calmodulin (CaM) binding domain and an autoinhibitory domain (AID) that interacts with the catalytic domain and inactivates the kinase (Cruzalegui and Means, 1993). (C) Association or C-terminal oligomerization domain is required for the assembly of subunits into a holoenzyme.

CaMKII has the capacity to retain a "memory" of its prior activation by Ca^{2+}/CaM because of a two step activation process. In the first step, which is similar to the activation process of the monomeric CaM kinases (Goldberg, et al., 1996, Mayans, et al., 1998), Ca^{2+}/CaM removes an auto-inhibitory/regulatory segment located at the C-terminal of the kinase domain. This un-masks the catalytic activity of the enzyme and makes it accessible to regulatory residue, Thr 286 (mouse CaMKII α isoforms numbering, used throughout the text). The second step is the phosphorylation of Thr 286 by another kinase domain within the oligomeric holoenzyme (Lai, et al., 1986, Lou and Schulman, 1989, Rich and Schulman, 1998, Schworer, et al., 1988, Zucker and Regehr, 2002). Phosphorylation of Thr 286 keeps CaMKII active in the absence of Ca^{2+}/CaM by preventing the rebinding of the regulatory segment to the kinase domain (Lai, et al., 1986, Yang and Schulman, 1999) and by increasing the affinity of CaM for the enzyme by 13,000-fold (Meyer, et al., 1992). Once a kinase subunit is activated by Ca^{2+}/CaM, it can phosphorylate adjacent subunits that are also bound to Ca^{2+}/CaM. If the concentration of Ca^{2+} is high, phosphorylation on Thr 286 will spread rapidly through the holoenzyme, leading to the onset of Ca^{2+}/CaM-independent activity. When the Ca^{2+} concentration is low, Thr 286 is dephosphorylated before activation can proceed. Regulated activation (Lisman, et al., 2002) and deactivation (Nelson, et al., 2005) of the enzymatic activity have both been shown to be important for the physiological function of CaMKII.

Calmodulin (CaM) is necessary for CaMKII activity:

Calcium ions play significant role in signal transduction pathways that control a variety of neuronal functions such as synaptic plasticity (Naoki, et al., 2005). There are many forms of synaptic plasticity; most are initiated by an increase in the intracellular Ca^{2+}, which function as a second messenger for activity dependent, synapse specific changes. Ca^{2+} signaling is mediated through several Ca^{2+}-binding proteins, including calmodulin (CaM). CaM is a regulatory protein that modulate the activity of several signaling molecules such as protein kinase C (PKC), phosphorylase kinase, myosin light chain kinase, calcineurin, and CaMK I, II, IV, that are crucial for synaptic plasticity (Xia and Storm, 2005). CaMKII is one of the calmodulin-regulated enzymes which plays an essential role in synap-

tic plasticity. Previous studies provide strong evidence that CaM serves as a key signalling protein in synaptic plasticity (PTP) and calmodulin is necessary for CaMKII activity. CaM is thought to be an important molecule that controls synaptic changes in terms of both potentiation (short- and long-term) and depression (Kandel, 2001, Lisman, et al., 2002, Malenka and Nicoll, 1999). Calmodulin has four Ca^{2+} binding sites. As calcium ions enter into the cell through the voltage- and ligand-gated calcium channels and bind with calmodulin, it brings about conformational change that increases the affinity of calmodulin for CaMKII (Schulman, 1993). In response to Ca^{2+}-calmodulin binding, the auto-inhibitory sequence is displaced leading to the activation of CaMKII. CaMKII subunits can autophosphorylate and, once autophosphorylation occurs, the enzyme is no longer Ca2+- calmodulin dependent (Schulman, 1993). The activity of CaMKII depends directly on the concentration of calcium-calmodulin complex (Castellani, et al., 2005).

Taken together, the literature cited above strongly suggest that calmodulin is essential for the activation of CaMKII, which in turn regulates synaptic transmission as well as PTP at the VD4-LPeD1 synapse (Luk, et al., 2011).

There are many forms of synaptic plasticity; most are initiated by an increase in the intracellular Ca^{2+}, which functions as a second messenger for activity dependent, synapse specific changes. Ca^{2+} signalling is mediated through several Ca^{2+}-binding proteins, including calmodulin (CaM). CaM is a regulatory protein that modulates the activity of several signaling molecules such as CaMKII, that are crucial for synaptic plasticity (Xia and Storm, 2005). CaMKII is inactive in the absence of Ca^{2+}/ calmodulin. Attachment of four calcium ion to calmodulin induces a conformational change that increases the affinity of calmodulin for CaMKII (Schulman, 1993). In response to Ca^{2+}-calmodulin binding, the auto-inhibitory sequence is displaced leading to the activation of CaMKII. CaMKII subunits can autophosphorylate and, once autophosphorylation occurs, the enzyme is no longer Ca^{2+}- calmodulin dependent (Schulman, 1993).

Synaptic transmission:

In addition to its myriad function in numerous cellular processes, Ca^{2+} also plays several critical roles in transmitter release. Synaptic transmission is the process of intercellular communication which is essential for understanding all nervous system functions – ranging from simple reflexes to complex motor patterns and learning and memory (Greengard, et al., 1993). Numerous studies demonstrate a direct role of CaMKII in synaptic transmission and strongly suggest that presynaptic activity of CaMKII is necessary for normal synaptic transmission.

The process of synaptic transmission is initiated with the arrival of an action potential at the nerve terminal, which permits Ca^{2+} influx through voltage-gated calcium channels and depolarizes the plasma membrane of the presynaptic neuron; the rise in intracellular Ca^{2+} in turn triggers the release of neurotransmitters into the synaptic cleft by the process of exocytosis. Presynaptic mechanism of neurotransmitter release involve a numbers of steps including mobilization of synaptic vesicles from a reserve pool to a readily releasable pool, docking of vesicles at the active zone, and the vesicle fusion with the plasma membrane. Various proteins associated with the membrane of synaptic vesicles, are phosphoproteins: for example, synapsin I, synaptophysin, synaptotagmin and vesicle associated membrane proteins (Greengard, et al., 1993, Sudhof and Jahn, 1991), and their functional role is modified by phosphorylation. Moreover this phosphorylation of synaptic vesicles associated proteins appears to play an essential role in regulating the release of neurotransmitters from nerve terminals. Presynaptically, CaMKII may modulate transmitter release by phosphorylating some synaptic vesicle-associated proteins, such as synapsin and actin filaments. Synaptophysin is also a substrate for CaMKII which phosphorylates synaptophysin on its serine residues (Rubenstein, et al., 1993). Genetic knockdown of these proteins results in disruption of presynaptic facilitation of transmitter release (Zucker and Regehr, 2002).

At low frequency (i.e. single action potentials) there is enough Ca^{2+} to induce transmitter release – however at higher frequencies much Ca^{2+} enters which can be effectively buffered by the intracellular buffering mechanisms. The cell would then need to respond to this free intracellular Ca^{2+} by coupling it to another signal amplification system such as CaMKII. Further studies are however required to define the precise relationship between Ca^{2+} and CaMKII. Moreover, the precise target proteins for CaMKII action and the underlying mechanisms still remain to be elucidated.

CaMKII in Synaptic Plasticity:

CaMKII is the most widely studied, multi-functional enzyme, which is highly expressed in forebrain such as hippocampus and cortex. In higher vertebrates and mammals, CaMKII function is restricted to postsynaptic cell where it is required for NMDA mediated synaptic plasticity.

Presynaptically, CaMKII may enhance vesicle release, phosphorylate synapsin I, (a protein on the surface of the synaptic vesicle) and can regulate the neurotransmitter release (Greengard, 1991). However, its precise function and the underlying presynaptic mechanisms have not yet been fully defined.

Synaptic transmission is initiated by exocytosis of docked vesicles at the active zone, which in turn result in the secretion of neurotransmitters into the synaptic cleft and subsequent activation of postsynaptic receptors (Fernandez-Chacon, et al., 2002). Synaptic vesicles have proteins in their membrane, for example, synapsin 1, synaptophysin, synaptotagmin and the vesicle associated membrane protein (VAMP)/synaptobrevin (SYB) (Greengard, et al., 1993, Sudhof and Jahn, 1991) which anchor, dock and probably fuse the synaptic vesicles with the plasma membrane. Presynaptically, CaMK II may modulate transmitter release by phosphorylating some synaptic vesicle-associated proteins, such as synapsin and actin filaments. Synaptophysin is also a substrate for CaMKII which is phosphorylated at its serine residues (Rubenstein, et al., 1993). Genetic knockdown of these proteins results in disruption of presynaptic transmitter release (Zucker and Regehr, 2002).

CaMKII is involved in numerous forms of synaptic plasticity like LTP (Gao, et al., 2006, Huang, et al., 1994, Malenka, et al., 1989, Miyamoto, 2006, Myers, et al., 2017, Wu, et al., 2006), LTD (Hansel, et al., 2006, Mulkey, et al., 1993, Stevens and Wang, 1994), PTP (Chapman, et al., 1995) and has also been shown to regulate the frequency-response function of the synapse underlying LTD and LTP (Mayford, et al., 1995).

LTP is triggered by a transient increase in the intracellular Ca2+ concentration, which activates the biochemical cascade leading to enhanced synaptic transmission (reviewed in, (Bliss and Collingridge, 1993, Nicoll and Malenka, 1999). Excitatory synaptic transmission in brain occurs at synapses that use glutamate as their neurotransmitter. This signaling is primarily mediated by two classes of glutamate gated ion channels, NMDA (N-methyl d-aspartate) and AMPA (α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid) receptors. Activity-dependent changes in AMPA receptor function represent a key mechanism for brain plasticity that underlies learning and memory. Long-term potentiation (LTP) in the hippocampal pyramidal cells is the best-established model for this plasticity. Although the molecular mechanisms for LTP are not fully defined, it is however, clear that Ca^{2+} influx through NMDA receptors initiates the changes seen during LTP (Lisman, 2003, Luthi, et al., 2004, Malenka and Bear, 2004, Nicoll and Malenka, 1999). The activation of calcium/calmodulin dependent protein kinase II (CaMKII) has also been shown to be necessary and sufficient for the expression of LTP (Hayashi, et al., 2000, Lledo, et al., 1995, Silva, et al., 1992). LTP increases both the number of synaptic AMPA receptors and their single-channel unitary conductance (Andrasfalvy and Magee, 2004, Benke, et al., 1998, Luthi, et al., 2004, Manabe, et al., 1992). AMPA receptors are heterotetramers, which are comprised of four subunits GluR1-4 (Dingledine, et al., 1999, Hollmann and Heinemann, 1994). A recent study by Oh and Derkach (Nelson, et al., 2005) suggests that CaMKII increases the single channel conductance of homomeric GluR1, but not that of the heteromeric GluR1/GluR2 channel. Taken together, the above studies suggest a potential role for CaMKII in long-term synaptic plasticity; however its involvement in short-term plasticity has not yet been documented.

CONCLUSIONS:

Taken together, CaMKII is required not only for normal synaptic transmission but it also play a key role in various form of synaptic plasticity including, LTP and STP. CaMKII activation is necessary and sufficient for synaptic transmission and synaptic plasticity. This review will advance our knowledge and understanding of the function of CaMKII and its involvement in synapse formation, synaptic transmission and synaptic Plasticity. Moreover, these studies have also identified the second messenger cascade underlying synaptic transmission and synaptic Plasticity.

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